PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 May 2001 (03.05.01)	
International application No. PCT/EP00/07726	**Applicant's or agent's file reference** 012M PCT 482
International filing date (day/month/year) 09 August 2000 (09.08.00)	**Priority date** (day/month/year) 10 August 1999 (10.08.99)
Applicant BERNARDELLI, Patrick	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

28 February 2001 (28.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
012M PCT 482		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/07726	09/08/2000	10/08/1999

International Patent Classification (IPC) or national classification and IPC
C07B33/00

Applicant
WARNER LAMBERT COMPANY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/02/2001	

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/07726

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-14	as originally filed				

Claims, No.:

1-17	as received on	09/10/2001	with letter of	08/10/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rul 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-7,9,10,12-14,17
	No:	Claims	1,8,11,15,16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Section I

D1 is considered to represent the closest prior art and discloses the oxidation of the benzodiazepine derivative Odapipam in the presence of a metalloporphyrin, an oxidizing agent and dichloromethane as inert aprotic polyhalogenated solvent (cf. page 14, scheme 8). In view of that disclosure it is clear that D1 cannot be considered as accidental disclosure. In the case of a non accidental disclosure the international examining authority is of the opinion, that a proviso based on the disclosure of that document shall not be allowed under Articles 19 and 34(2)b) PCT. The reason is that the teaching of the originally filed application is to use an inert aprotic solvent selected from a polyhalogenated aliphatic or aromatic solvent, but not an inert aprotic solvent selected from a polyhalogenated aliphatic or aromatic solvent with the proviso that the inert aprotic solvent is not dichloromethane, dichloroethane or trichloroethane. Thus, the amendments made, go beyond the subject matter as originally filed.

Therefore, in accordance with Rule 70.2c) the international preliminary examination report is drawn up as if the amendments which extend beyond the content of the application as originally filed have not been made.

Section V

D1: WO-A-96 08455
D2: EP-A-0 342 615
D4: CHEMISTRY LETTERS, no. 8, 1998, pages 837-838

Novelty

The present application is directed to a process for the oxidation of organic compounds and comprises reacting the organic compound to be oxidized with a reaction medium comprising a metalloporphyrin and an oxidizing agent in an inert aprotic solvent selected from a polyhalogenated aliphatic or aromatic solvent, and recovering and identifying the desired reaction products.

D1 is considered to represent the closest prior art and discloses the oxidation of the benzodiazepine derivative Odapipam and is novelty destroying for the subject matter of

claim 1 (cf. claim 1 and page 8, lines 7-14, page 14, scheme 8).
D2 relates to the preparation of epoxides and is also novelty destroying for the subject matter of claims 1, 8, 11, 15, 16 (cf. examples 1 and claims).
D4 is also novelty destroying for the subject matter of claim 1 (cf. the whole document).

Thus, the subject matter of claims 1, 8, 11, 15, 16 does not fulfil the requirements of Article 33(2) PCT.

However, the special features defined in claims 2-7, 9, 10, 12-14 and 17 are not disclosed in the available prior art.

Inventive step

The technical problem may be regarded as the provision of an alternative process for the oxidation of organic compounds.
From the present claims it appears that any thinkable organic compound might be oxidized by the presently claimed process. However, the process is only illustrated by using the group of benzodiazepine derivatives as examples. Therefore, in the absence of an additional data showing unambiguously that other organic compounds may be oxidized via the proposed process e.g. benzene, toluene etc. the process proposed, can only be considered to be a solution of the above stated technical problem for the group of benzodiazepines.

Apart from that, the subject matter of the present application can also not be considered to involve an inventive step in view of D1 (cf. Section I).

Thus, the subject matter of claims 1-17 is not fulfilling the requirements of Article 33(3) PCT.

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D4 is not mentioned in the description, nor are these documents identified therein.

CLAIMS

1) A process for the oxidation of an organic compound, said process comprising reacting the organic compound to be oxidized with a reaction medium comprising a metalloporphyrin and an oxidizing agent in an inert aprotic solvent selected from a polyhalogenated aliphatic or aromatic solvent,and recovering and identifying the desired reaction products,
with the proviso that the inert aprotic solvent is not dichloromethane, dichloroethane or trichloroethane.

2) Process according to claim 1, wherein the inert aprotic solvent is a polyhalogenated aromatic solvent.

3) Process according to claim 2, wherein the solvent is trifluorotoluene.

4) Process according to claim 1, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent capable of increasing the solubility of the organic compound in the reaction medium.

5) Process according to claim 4, wherein said co-solvent is a polar and poorly nucleophilic solvent.

6) Process according to claim 5, wherein said solvent is 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-propan-2-ol.

7) Process according to claim 4, wherein the concentration of the co-solvent ranges between 1 and 30%.

8) Process according to claim 1, wherein said reaction medium comprises a biphasic solution.

9) Process according to claim 8, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the organic compound from one phase to the other.

10) Process according to claim 9, wherein the co-solvent is hexafluoroisopropanol.

11) Process according to claim 8, wherein said reaction medium includes a

first aqueous phase comprising the oxidizing agent and a second organic phase comprising the organic compound and a metalloporphyrin in an inert aprotic solvent.

12) Process according to claim 11, wherein said second phase comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the oxidizing agent from one phase to the other.

13) Process according to claim 12, wherein said co-solvent is water-miscible.

14) Process according to claim 12, wherein said co-solvent is 1,1,1,3,3,3-hexafluoro-propan-2-ol.

15) Process according to claim 8, which comprises introducing a phase-transfer catalyst into the reaction medium, said phase-transfer catalyst having the capability of allowing the transfer of reactants from one phase to the other.

16) Process according to claim 15, wherein the phase-transfer catalyst is a tetraalkyl ammonium salt.

17) Process according to claim 16, wherein the tetraalkyl ammonium salt is dodecyl-trimethyl–ammonium bromide.

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/10797 A1

(54) Title: PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

(57) Abstract: Oxidation of organic compounds is catalyzed by addition of a catalytic amount of a metalloporphyrin in a non-reactive aprotic solvent.

PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

FIELD OF THE INVENTION

The study of drug metabolism is an important part of the very expensive drug R&D process. In humans and other mammals, many drugs are metabolized through oxidative reactions catalyzed by heme- and cytochrome-containing enzymes. Cytochrome P450 mono-oxygenases, the main enzymes involved in drug oxidative metabolism, have in their active site a heme moiety.

Synthetic metalloporphyrins can serve favorably to mimic oxidative catalytic reactions occurring in biological systems, with the aim of producing and identifying oxidative products of drug candidates, in quantities allowing in vivo studies.

PCT application WO 96/08455 discloses a process for the preparation of oxidative products using various combinations of a synthetic metalloporphyrin, a co-oxidizing reagent, and a solvent. The solvent is generally a CH_3CN/CH_2Cl_2 combination. One of the major inconveniences of processes of this type is the fact that they frequently provide incomplete yields of the sought-after individual products as well as low conversion percentages. As a result, they can rarely be used in a reliable fashion in integrated discovery processes. In fact, their use is generally limited to experimental validation.

SUMMARY OF THE INVENTION

In accordance with the present invention, the inventor has unexpectedly found that the yields of oxidative reactions involving metalloporphyrins and which can be useful for the synthesis of metabolites of organic compounds of interest could be increased in a substantial manner through the use of an inert aprotic solvent.

Thus, one of the objects of the present invention is a process for the oxidation of organic compounds. This process comprises reacting the selected organic compound with catalytic amounts of a metalloporphyrin and of an oxidizing agent in the presence of an inert aprotic solvent and recovering the desired products obtained therefrom.

The process of the invention is extremely useful in pharmaceutical research and development as it can be used to perform preliminary evaluations of the metabolic processes which are likely to occur when a given compound is tested in vivo. These preliminary evaluations can be performed rapidly without having to carry out expensive and time consuming in vivo experiments. Furthermore, the process of the present invention provides better yields of individual products than those obtained using prior art processes. In other words, the process of the present invention opens the possibility of obtaining and analyzing in a more systematic fashion a higher number of individual potential metabolites for a given selected compound on which the process is carried out.

DETAILED DESCRIPTION OF THE INVENTION

The present invention therefore concerns a process for the efficient oxidative preparation of metabolites of organic compounds. The invention comprises reacting an organic compound of interest with a catalytic amount of a metalloporphyrin and an oxidizing agent, in a non-reactive aprotic solvent. It also comprises recovering and identifying the desired reaction products.

As mentioned previously, several drugs are metabolized through oxidative reactions. The process of the instant invention is therefore applied favorably to organic compounds of interest possessing one or several functional groups which will react to oxidation conditions. Some of these functional groups are described below but as the skilled person will readily appreciate, the list provided is not intended to be exhaustive. In fact, the process of the invention can be used on any organic compound which can be oxidized in some way by enzymes involved in drug oxidative metabolism.

Preferably, compounds containing heteroatoms, such as nitrogen or sulfur, can be efficiently oxidized through the process of the invention, particularly to a higher oxidation state, and more particularly to their highest oxidation state. For example, primary amines can be readily converted to their corresponding hydroxylamines, nitroso- or nitro- derivatives; and tertiary amines to their corresponding *N*-oxides.

Also, C-H bonds can be conveniently hydroxylated into C-OH bonds by metalloporphyrin-catalyzed oxidations according to this invention. Examples include labile C-H bonds, such as

those in benzylic positions or C-H bonds wherein the carbon atom is adjacent to a heteroatom (e.g. N, S, O, or the like). Those are particularly reactive to these conditions. In this manner, primary alcohols can be converted to their corresponding aldehydes; in turn aldehydes can be converted to their corresponding acids, and said acids may further undergo decarboxylation.

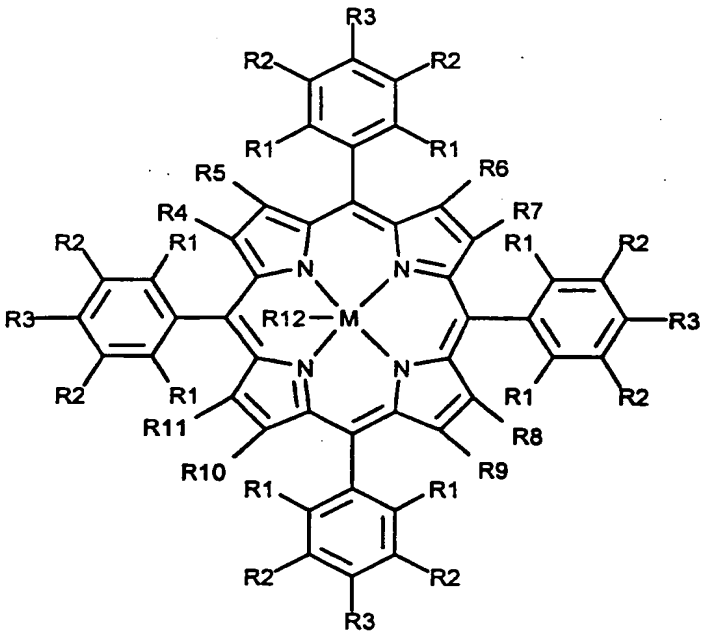
Through the process of the invention, secondary alcohols can be converted to their corresponding ketones.

Carbon-carbon double bonds can be epoxidized by metalloporphyrin-catalyzed oxidation according to this invention, and aromatic groups can be oxidized into corresponding phenols or quinones.

The main parameters involved in the process of the invention are the starting material which is usually an organic compound of interest, the reactants which usually include a metalloporphyrin, an oxidizing agent and an inert aprotic solvent, and the reaction conditions which comprise the reaction temperature and the reaction time. Each of these parameters will be discussed in further detail below.

Metalloporphyrins

Synthetic metalloporphyrins are described in international patent application WO 96/08455. The term "metalloporphyrin", as used herein, refers to porphyrin compounds of formula (I):



wherein:

R1, R2 and R3 independently represent hydrogen or an electron-withdrawing group such as Cl, F, Br, SO_3Na, or the like,

R4, R5, R6, R7, R8, R9, R10 and R11 independently represent hydrogen or an electron-withdrawing group such as Cl, F, Br, NO_2, CN, SO_3Na or the like,

R12 is Cl, acetate or the like,

M is selected from the group consisting of iron, manganese, chromium, ruthenium, cobalt, copper and nickel.

Preferred metalloporphyrins include tetrakis(pentafluoro-phenyl)porphyrin Mn(III) chloride, herein abbreviated as Mn(TPFPP)Cl, which is the compound of formula (I) above wherein M is manganese, R1, R2 and R3 are fluorine, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine.

Preferred metalloporphyrins also include:

tetrakis(pentafluoro-phenyl)porphyrin Fe chloride, abbreviated as Fe(TPFPP)Cl, which is the compound of formula (I) above wherein M is iron, R1, R2 and R3 are fluorine, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)porphyrin Mn chloride, abbreviated as Mn(TDCPP)Cl, which

is the compound of formula (I) above wherein M is manganese, R1 is chloride, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)porphyrin Fe chloride, abbreviated as Fe(TDCPP)Cl, which is the compound of formula (I) above wherein M is iron, R1 is chloride, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)-octachloroporphyrin chloride Fe, abbreviated as $Fe(TDCPCl_8P)Cl$, which is the compound of formula (I) above wherein M is iron, R1 is chloride, R2 and R3 are hydrogen, R4, R5, R6, R7, R8, R9, R10 and R11 are chloride, and R12 is chlorine;

the compound $Mn((Cl_2Ph)_4\ (NO_2)P)Cl$, of formula (I) above wherein M is manganese, R1 is chloride, R4 is NO2, R2, R3, R5, R6, R7, R8, R9, R10, and R11 are hydrogen, and R12 is chlorine;

the compound $Mn((Cl_2Ph)_4(NO_2)_2P)Cl$, of formula (I) above wherein M is manganese, R1 is chloride, R5 and R6 are NO_2, R2, R3, R4, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine.

The amount of the metalloporphyrin catalyst usually ranges between 0.5 and 10 % molar and is preferably about 1 % molar.

Oxidizing agents

Various oxidizing agents can be used in the instant invention. It should be noted that the very nature of the oxidizing agent does not appear to be a limiting factor in the process of the present invention. The person skilled in the art can thus select the appropriate oxidizing agent among the wide variety of compounds which have been used in metalloporphyrin-catalyzed oxidative reactions. A list of possible agents includes, but is not limited to: iodosylbenzene, also known as iodosobenzene, aqueous solutions of hydrogen peroxide (concentration about 30 to 45 %), anhydrous equivalents of hydrogen peroxide such as sodium percarbonate, urea hydrogen peroxide complex or the like, potassium monopersulfate, sodium hypochlorite, *tert*-butyl hydroperoxide, cumene hydroperoxide, *m*-

chloroperbenzoic acid, and magnesium monoperoxyphthalate. Preferred oxidants include iodosylbenzene, any source of hydrogen peroxide, and potassium monopersulfate.

Oxidation using hydrogen peroxide is more efficient in the presence of a co-catalyst such as imidazole, ammonium acetate, *N*-hexylimidazole, amine *N*-oxides, tetrabutylammonium acetate, *tert*-butyl pyridine, pyridine, 4-methylpyridine, and 2,4,6-trimethyl-pyridine. For a review, see "State of the art in the development of biomimetic oxidation catalysts" Rocha Gonsalves, A.M.; Pereira, M.M. *J. Mol. Catal. A: Chem.* **1996**, *113*, 209.

Solvent

The metalloporphyrin-catalyzed oxidation of the invention is performed in an inert solvent, which in fact can contain one or several solvents. The term 'inert aprotic solvent', when used herein, is intended to designate any solvent or any mixture of solvents which, when evaluated in a global manner, does not react in any substantial fashion with the starting materials or with the products of the reaction. More particularly, the solvent should not react with the oxidizing agent. Furthermore, the solvent should be resistant to hydrogen abstraction.

In the case of a mixture of solvents, this mixture usually contains a so-called "main solvent" and a "co-solvent". It should be noted however that several solvents having similar properties could be used to form the main solvent. Similar considerations apply to an eventual mixture of co-solvents.

The main solvent is present in larger amounts in the solvent mixture than the co-solvent.

In fact, it is the main solvent that confers its overall properties to the global solvent mixture, which will then play a key role in the process of the invention. The main solvent should therefore be inert and aprotic.

To the extent possible, the main solvent should have the capability to dissolve the starting material (i.e. the organic compound of interest) and the metalloporphyrin.

Examples of the main solvent include, but are not limited to polyhalogenated aliphatic solvents such as 1,1,2-trichloro-1,2,2-trifluoroethane and the like or polyhalogenated

aromatic solvents such as 1,2-dichlorobenzene, 1,2,4-trichlorobenzene, pentafluorobenzene and the like. Preferred polyhalogenated solvents include polyfluorinated aromatic compounds, such as trifluorotoluene (also known as benzotrifluoride) and the like. Trifluorotoluene is a most preferred solvent, which combines the capacity of dissolving a wide variety of organic compounds with a low reactivity towards oxidative conditions.

Although the skilled person can determine by routine experiments the optimal amount of main solvent to be used in each individual case, suitable concentrations of starting material in the chosen solvent can vary between 0.1 M and 0.5 M, preferably 0.1 M.

The co-solvent is present in small amounts in the mixture and is introduced to provide additional properties of interest to the overall solvent mixture, which will be useful at some point but which will not interfere in a significant manner with the reaction itself.

In a first embodiment of the process of the present invention, if any of the organic compound of interest or the oxidizing agent is not soluble in the main solvent, a co-solvent can be used to improve its solubility in the reaction medium.

For example, if the starting material is not soluble in trifluorotoluene or in any main solvent available, a co-solvent can be used in order to improve its solubility in the reaction medium. Preferred co-solvents include highly polar and poorly nucleophilic co-solvents. Preferably, the properties of the co-solvent should be chosen in order to minimize complex formation with the metalloporphyrin. 2,2,2-Trifluoroethanol and, particularly, 1,1,1,3,3,3-hexafluoro-propan-2-ol (also called hexafluoroisopropanol or HFIP) are representative examples of co-solvents that can be used in the process of this invention. More particularly, hexafluoroisopropanol, can be useful in oxidation reactions performed with iodosylbenzene in one of the organic solvents mentioned above since this co-solvent helps dissolve this particular oxidant in the reaction medium.

The amount of co-solvent used to dissolve the starting material or the oxidizing agent and eventually the catalyst should be kept to relatively low levels with respect to the main solvent. Although the skilled person can determine by routine experiments the optimal amount of co-solvent to be used in each individual case, suitable concentrations can vary between 1 and 30%, preferably between 1 and 20% and more preferably between 1 and 10%

with respect with the main solvent.

In a second embodiment of the process of the present invention, the co-solvent can be used in order to facilitate transfer of reactants within the reaction medium. For instance, a co-solvent is used in the case where the starting material or one or several reactants leads to a reaction mixture which comprises a biphasic solution.

For example, in the case where the oxidant is used as an aqueous solution, the reaction is biphasic and a water-miscible co-solvent can be used to facilitate the transfer of the oxidant in the organic phase. A minimal amount of co-solvent, such as hexafluoroisopropanol, is preferred. This co-solvent is miscible with water and it can facilitate dissolution of the starting material.

The amount of co-solvent which should be used in this second embodiment, as expressed in catalytic amounts, usually ranges between 0.25 and 1 equivalent, preferably between 0.3 and 0.5 and is more preferably about 0.4 equivalent with respect to the starting material.

As an alternative to this second embodiment of the invention, a phase-transfer catalyst can be used to facilitate the transfer of any of the reactants into the phase where the reaction will take place. For instance, when the oxidant is used as an aqueous solution, a phase-transfer catalyst can be used to facilitate the transfer of the oxidant in the organic phase.

Examples of phase-transfer catalysts include tetraalkyl ammonium salts (such as dodecyl-trimethyl-ammonium bromide and the like). The amount of phase-transfer catalyst which should be used in this second embodiment, as expressed in catalytic amounts, usually ranges between 0.05 and 0.5 equivalent and is more preferably about 0.10 equivalent with respect to the starting material.

Temperature and duration of the reaction

The reaction is carried out at a temperature between about -20 °C and 100 °C, and preferably between about -10 °C and 40 °C.

The skilled person should note however that sonication can be used to increase the reaction rate. The reaction is then preferably performed in an ultrasound bath cooled to

0°C.

Generally, the duration of the reaction varies from a few minutes up to 2 h. Advancement can be monitored with TLC or HPLC analytical techniques; thus the reaction is stopped when the oxidation reaction reaches a plateau point beyond which no substantial conversion is observed.

EXAMPLES

Without limiting the invention, the following examples illustrate the implementation of the processes of the invention.

The purity, identity and physico-chemical characteristics of the products prepared are determined as follows:

- the purity is verified by analytical reverse-phase HPLC on a Merck Lachrom apparatus and the Rf observed is given for the eluent used;

- the identity of the products obtained with the proposed structures is verified by their proton nuclear magnetic resonance spectrum and by mass spectrometry.

The ^1H NMR spectra are recorded at 400 MHz on a Brüker instrument, the compounds being dissolved in deuterochloroform with tetramethylsilane as internal standard. The nature of the signals, their chemical shifts in ppm, the number of protons they represent and their exchange capacity with D_2O are noted.

The mass spectra are recorded on a Micromass Platform LC spectrometer (simple quadrupole with positive ionization electrospray). The infrared spectra are recorded on a Nicolet spectrometer.

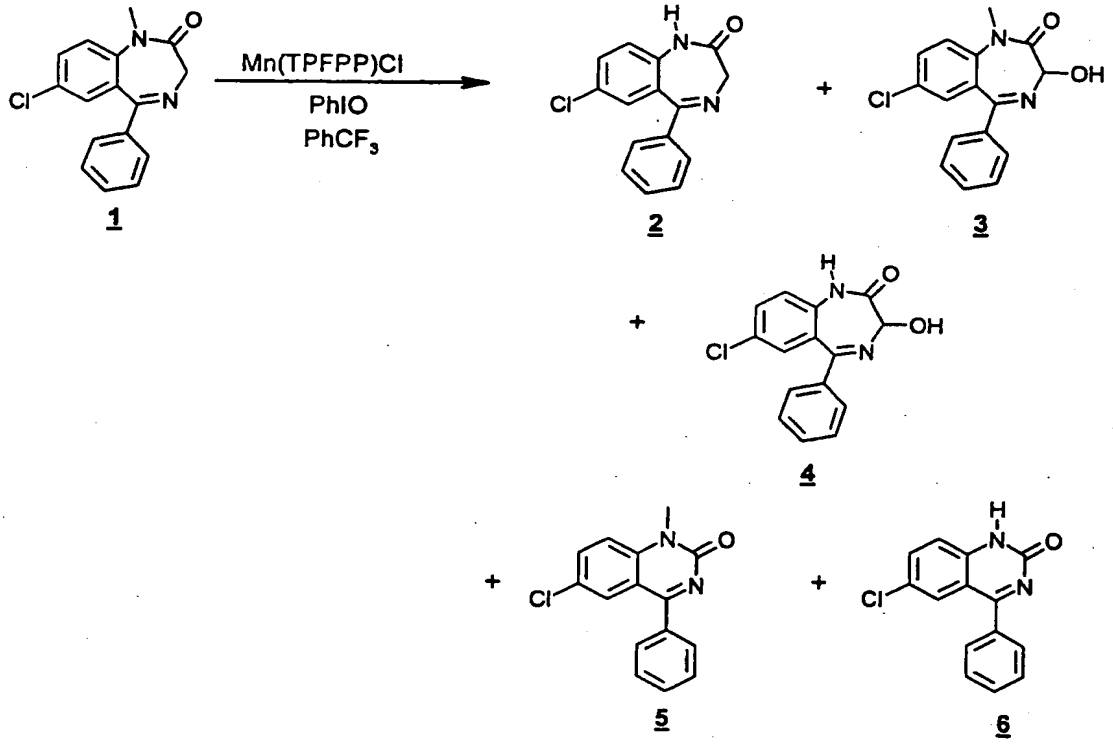
The phrase "flash chromatography on a silica column" means a method adapted from that of Still *et al.* (1978) J. Org. Chem. 43: 2923. The purity of elution fractions is verified before they are gathered and evaporated.

The terms "evaporation", "elimination" or "concentration" of the solvents mean, possibly after desiccation on an appropriate dehydrating agent such as Na_2SO_4 or $MgSO_4$, a distillation under a pressure of 25 to 50 mm Hg (3,3 to 6,7 kPa) with moderate heating in a water bath at a temperature below 30 °C.

EXAMPLE 1

Oxidation of diazepam (1) with iodosylbenzene (PhIO) catalyzed by tetrakis(pentafluorophenyl)porphyrin manganese (III) chloride in trifluorotoluene.

During this reaction, nordiazepam (2), temazepam (3), oxazepam (4), 6-chloro-4-phenyl-1-methyl-2-(1*H*)-quinazolinone (5) and 6-chloro-4-phenyl-2-(1*H*)-quinazolinone (6) are formed.



1 2 3 4 5 6

To 240 µL of a solution containing 25 µmol of diazepam (1) in trifluorotoluene is added 10 µL of a 25 mM solution of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin manganese (III) chloride (0.25 µmol, 1 mol%) in trifluorotoluene. To the resulting stirring solution is added 3 times a portion of iodosylbenzene (3x5.5 mg, 3x25 µmol, 3 equiv.), one every hour. The reaction is monitored by analytical HPLC one hour after each addition: a

sample, prepared with 5 μL of crude and 100 μL of a 5 mM methanolic solution of acetophenone (internal standard) diluted with 395 μL of methanol, is injected into a Nucleosil 5C18 150x4.6 mm column eluting with 50/50 methanol/water at 1 mL/min during 45 minutes. Nordiazepam (**2**), temazepam (**3**), oxazepam (**4**) formed are identified by comparison with authentic samples (Sigma). Their retention times are respectively 21.9, 16.7 and 13.3 min. 6-Chloro-1-methyl-4-phenyl-1*H*-quinazolin-2-one (**5**) and 6-chloro-4-phenyl-1*H*-quinazolin-2-one (**6**), respectively eluting at 25.1 and 20.5 min, are identified in a separate run by isolation and comparison of ^{1}H NMR and MS data with Felix *et al* (1968) *J. Heterocycl. Chem.* 5, 731 and Sulkowski *et al* (1962) *J. Org. Chem.* 27, 4424.

Yields of products from the reaction are shown in the following table:

PhIO	Products obtained: Yield (%)					
(equiv.)	**1**	**2**	**3**	**4**	**5**	**6**
1	31	19	12	3	4	0
2	5	17	6	7	11	4
3	1	9	2	5	10	3

Results form the reaction performed in 1:1 CH_2Cl_2/CH_3CN, solvent conditions representative of the state of the art, are shown below:

PhIO	Products obtained: Yield (%)		
(equiv.)	**1**	**2**	**3**
1	86	1	1
2	83	1	2
3	79	1	2

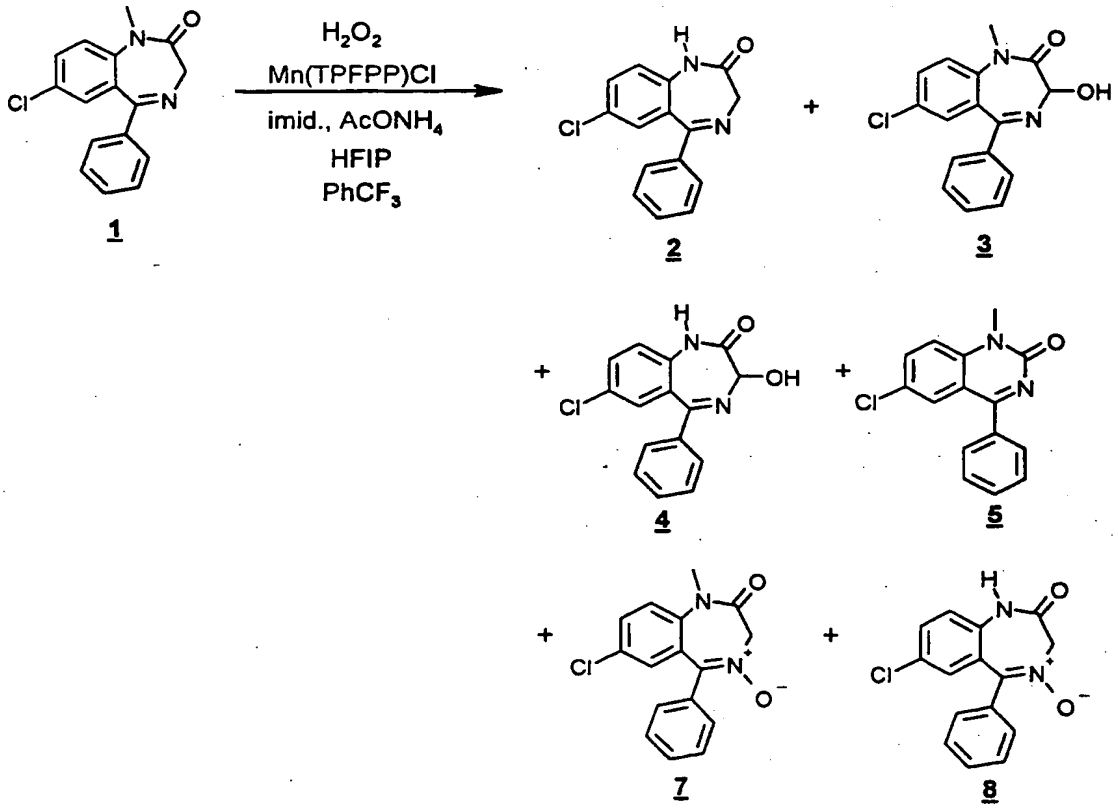
Comparison of both sets of results implies that the use of a solvent such as trifluorotoluene instead of the classical dichloromethane/acetonitrile leads to better diazepam conversion, and formation of a higher number of products in significantly better yields.

EXAMPLE 2:

Oxidation of diazepam (1) with a 30% aqueous solution of hydrogen peroxide catalyzed by tetrakis(pentafluorophenyl)porphyrin manganese (III) chloride in trifluorotoluene

This reaction is more efficient in the presence of catalytic amounts of imidazole (Battioni *et al* (1988) *J. Am. Chem. Soc.* 110, 8462) and ammonium acetate (Thellend *et al* (1994) *J. Chem. Soc., Chem. Comm.*, 1035).

During this reaction, nordiazepam (2), temazepam (3), oxazepam (4), 6-chloro-4-phenyl-1-methyl-2-(1*H*)-quinazolinone (5), diazepam *N*-oxide (7) and nordiazepam *N*-oxide (8) are formed.



To 240 µL of a solution containing 25 µmol of diazepam (1) in trifluorotoluene is added 10 µL of a 25 mM solution of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin manganese (III) chloride (0.25 µmol, 1 mol%) and 1,1,1,3,3,3-hexafluoro-2-propanol (1.1

μL, 10.4 μmol, 0.4 equiv.) in trifluorotoluene. To the resulting stirring solution is added dropwise an aqueous solution of 30% hydrogen peroxide (2.6 μL, 25 μmol, 1 equiv.), imidazole (6.5 μL of a 1 M aqueous solution, 6.5 μmol, 0.25 equiv.) and ammonium acetate (25 μL of a 1 M aqueous solution, 25 μmol, 1 equiv.) over two hours. Thirty minutes after the addition, the reaction is monitored by analytical HPLC in the same manner as in Example 1. One equivalent of 30% aqueous hydrogen peroxide (2.6 μL, 25 μmol, 1 equiv.) is then added every 10 minutes until 15 equivalents of oxidant are used. The reaction is monitored after the addition of 2, 5, 10 and 15 equiv. of hydrogen peroxide. Diazepam *N*-oxide (**7**) (retention time 8.4 min) and nordiazepam *N*-oxide (**8**) (6.7 min) are identified by comparison with samples prepared from the reaction of diazepam and nordiazepam with *m*-chloroperbenzoic acid (*cf.* Ebel *et al* (1979) *Arzneim.-Forsch.* 29, 1317).

Yields of products from the reaction are shown in the following table:

H_2O_2 (equiv.)	Products obtained: Yield (%)						
	1	**2**	**3**	**4**	**5**	**7**	**8**
1	71	4	7	0	1	5	0
2	58	8	10	1	1	9	1
5	41	10	13	1	3	10	1
10	26	10	12	2	5	8	2
15	19	10	14	2	8	6	2

Results form the analogous reaction performed in 1:1 CH_2Cl_2/CH_3CN, instead of trifluorotoluene and hexafluoroisopropanol as co-solvent, are shown below:

H_2O_2 (equiv.)	Products obtained: Yield (%)			
	1	**2**	**3**	**7**
1	84	1	1	2
2	77	2	1	3
5	74	5	3	6
10	74	6	7	7
15	74	5	9	7

When the oxidation is performed with hydrogen peroxide in a biphasic system, better diazepam conversion and yields in products are obtained with trifluorotoluene in the presence of hexafluoroisopropanol in place of the dichloromethane/acetonitrile solvent system.

Preliminary results from additional experiments currently underway confirm the efficacy of the process of the invention for the oxidation of compounds with relatively different structural parameters.

CLAIMS

1) A process for the oxidation of a selected organic compound, said process comprising reacting the selected organic compound to be oxidized with a reaction medium comprising a metalloporphyrin and an oxidizing agent in an inert aprotic solvent and recovering and identifying the desired reaction products.

2) Process according to claim 1, wherein the inert aprotic solvent is a polyhalogenated aliphatic or aromatic solvent.

3) Process according to claim 2, wherein the inert aprotic solvent is a polyhalogenated aromatic solvent.

4) Process according to claim 3, wherein the solvent is trifluorotoluene.

5) Process according to claim 1, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent capable of increasing the solubility of the selected organic compound in the reaction medium.

6) Process according to claim 5, wherein said co-solvent is a polar and poorly nucleophilic solvent.

7) Process according to claim 6, wherein said co-solvent is 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-propan-2-ol.

8) Process according to claim 5, wherein the concentration of the co-solvent ranges between 1 and 30%.

9) Process according to claim 1, wherein said reaction medium comprises a biphasic solution.

10) Process according to claim 9, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the selected organic compound from one phase to the other.

11) Process according to claim 10, wherein the co-solvent is hexafluoroisopropanol.

12) Process according to claim 9, wherein said reaction medium includes a first aqueous phase comprising the oxidizing agent and a second organic phase comprising the selected organic compound and a metalloporphyrin in an inert aprotic solvent.

13) Process according to claim 12, wherein said second phase comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the oxidizing agent from one phase to the other.

14) Process according to claim 13, wherein said co-solvent is water-miscible.

15) Process according to claim 13, wherein said co-solvent is 1,1,1,3,3,3-hexafluoro-propan-

2-ol.

16) Process according to claim 9, which comprises introducing a phase-transfer catalyst into the reaction medium, said phase-transfer catalyst having the capability of allowing the transfer of reactants from one phase to the other.

17) Process according to claim 16, wherein the phase-transfer catalyst is a tetraalkyl ammonium salt.

18) Process according to claim 17, wherein the tetraalkyl ammonium salt is dodecyl-trimethyl–ammonium bromide.

INTERNATIONAL SEARCH REPORT

Interna... Application No
PCT/EP 00/07726

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B33/00 C07B41/00 //C07D243/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 08455 A (ABBOTT LABORATORIES) 21 March 1996 (1996-03-21) cited in the application page 8, line 7 - line 14; claims; examples	1,2
X	YOON JING LEE: "Epoxidation of olefins with H2O2 catalyzed by an electronegatively-substituted iron porphyrin complex in aprotic solvent" CHEMISTRY LETTERS, no. 8, August 1998 (1998-08), pages 837-838, XP002156313 TOKYO JP the whole document	1
X	EP 0 342 615 A (ISTITUTO GUIDO DONEGANI) 23 November 1989 (1989-11-23) claims; examples	1,2,9, 12,16,17

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 January 2001	16/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wright, M

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INTERNATIONAL SEARCH REPORT

Interna. al Application No
PCT/EP 00/07726

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 41 01 334 A (CHEMIE AG BITTERFELD-WOLFEN) 8 August 1991 (1991-08-08) claims; examples	1

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 00/07726

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608455 A	21-03-1996	US 5760216 A	02-06-1998
		GA 2195873 A	21-03-1996
		EP 0781261 A	02-07-1997
		JP 10507442 T	21-07-1998
EP 342615 A	23-11-1989	IT 1217608 B	30-03-1990
		JP 2062870 A	02-03-1990
DE 4101334 A	08-08-1991	DD 291748 A	11-07-1991
		CH 681721 A	14-05-1993
		FR 2657606 A	02-08-1991

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
012M PCT 482		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 07726	09/08/2000	10/08/1999
Applicant		
WARNER LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07726

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B33/00 C07B41/00 · //C07D243/16

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B. FIELDS SEARCHED

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IPC 7 C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 January 2001	16/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wright, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07726

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/07726

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608455 A	21-03-1996	US 5760216 A	02-06-1998
		CA 2195873 A	21-03-1996
		EP 0781261 A	02-07-1997
		JP 10507442 T	21-07-1998
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		JP 2062870 A	02-03-1990
DE 4101334 A	08-08-1991	DD 291748 A	11-07-1991
		CH 681721 A	14-05-1993
		FR 2657606 A	02-08-1991